REMARKS

Claims 1-65 are pending. New claims 58-65 have been added. Claims 9-43 have been withdrawn from further consideration as being drawn to non-elected inventions. Claims 1, 2, 5-8, 50-57 have been amended.

Applicants respectfully assert that all amendments are supported by the original disclosure and do not introduce new matter. Moreover, Applicants further respectfully assert that the amendments merely clarify the scope of the claims.

The Examiner contends that claims 58 and 64 are directed to an invention that is independent or distinct from the invention originally claimed and are now withdrawn.

The Examiner contends that claims 1-8, 44-57, 59-63 and 65 are under examination. Due to restriction and species election, claims are examined to the extent that the inner leaflet component is phosphatidylserine, phosphatidylethanolamine, or a structure analog of phosphatidylserine wherein the structure analog of phosphatidylserine is dioleoylphosphatidylserine.

Interview Summary

Applicants thank Examiner Sang for the in-person interview, which took place on Thursday, September 4, 2008. The Examiner and Applicants discussed the outstanding rejections, particularly the 112 second paragraph and prior art rejections.

Applicant discussed that the terms raised by the Examiner, such as the relationship between the structure of the Saposin C polypeptide and its function. Applicants agreed to provide references available prior to the filing date of the present application clarifying the state of the art at the time of filing.

Examiner made suggestions for clarifying the claim language. No agreement on the exact claim language was reached but Applicant agreed to file a response to address the concerns of the Examiner.

Withdrawal of Rejection

Applicants appreciate Examiner's withdrawal of the rejection of claims 44-49 under 35 U.S.C. 112, second paragraph because of lack antecedent basis is withdrawn in view of applicant's amendment to the claims.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

The Examiner has maintained the rejection of claims 1-8, 50-57, and new claims 59-63 and 65 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner contends that Applicant's earlier arguments are not persuasive. The Examiner contends that the specification lacks written description regarding which amino acids and how many amino acids within the full length of SEQ ID NO.1 or 2 can be changed by a certain degree and certainly by conservative substitution such that the resulting variant has the claimed function (retaining plasma-membrane affinity).

The Examiner points out that Qi's publication (3/11/2004) discloses that the plasma membrane affinity is contained in the fusogenic domain of SEQ ID NO.1 or 2, this information was published after the effective filing date of the instant application.

Applicants apologize for any confusion resulting from this paper. Attached are references J. Biol. Chem., Vol. 271, No. 12, pp. 6874–6880, 1996, and J. Biol. Chem., Vol. 276, No. 29, pp. 27010–27017, 2001, showing that the structure of the Saposin C molecule has 5 helices, which was well-defined at the time the present application was filed.

In the present case, the specification identifies that the domains responsible for activity, *i.e.*, a plasma membrane binding domain, is made up of the H-1 and H-5 helices in SEQ ID NO: 2.

The disclosure of SEQ ID NO: 1 and SEQ ID NO: 2 combined with pre-existing knowledge in the art regarding the genetic code and its redundancies would have put one in possession of the genus of nucleic acids that encode SEQ ID NO: 2. With the aid of a computer, one of skill in the art could identify all of the nucleic acid sequences that encode a polypeptide with at least 95% sequence identity with SEQ ID NO: 2. However, there is no teaching regarding which 5% of the amino acids can vary from SEQ ID NO: 2 and still result in a protein that

retains activity. Further, the art-recognizes the correlation between the H-1 and H-5 helical structure of SEQ ID NO: 2 and novel activity.

General knowledge in the art includes the knowledge that some amino acid variations are tolerated without losing a protein's tertiary structure. The results of amino acid substitutions have been studied so extensively that amino acids are grouped in so-called "exchange groups" of similar properties because substituting within the exchange group is expected to conserve the overall structure. For example, the expectation from replacing leucine with isoleucine would be that the protein would likely retain its tertiary structure.

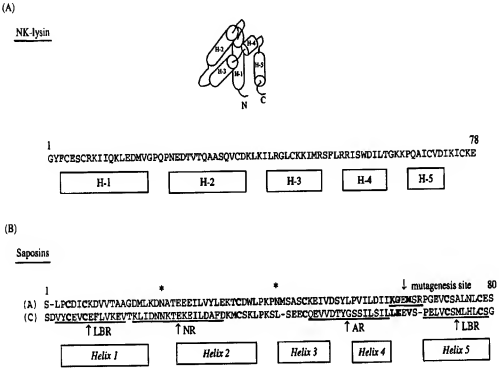
Given what is known in the art about the likely outcome of substitutions on structure, those in the art would have likely expected the applicant to have been in possession of a genus of proteins having a tertiary structure similar to SEQ ID NO: 1 and SEQ ID NO: 2 although the claim is not so limited.

Even given that conservation of structure is not necessarily a surrogate for conservation of function, the need for correlating information can vary. More specifically, those of skill in the art might require more or less correlating information depending on the kind of protein activity. If activity is simply structural, e.g., a member of the collagen class, correlating information may not be a critical factor. In contrast, if activity is enzymatic, and there is no disclosure of the active site amino acid residues responsible for the catalytic activity, lack of that kind of correlating information may be an additional item to consider. Here, the activity of the polypeptide is structural and is well described in the art.

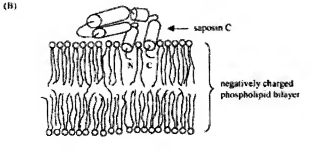
The specification also predicts that conservative mutations in these domains will result in a protein having activity. Although all conservative amino acid substitutions in these domains will not necessarily result in a protein having activity, those of ordinary skill in the art would expect that many of these conservative substitutions would result in a protein having the required activity. Further, amino acid substitutions outside of the two identified functional domains are unlikely to greatly affect activity. Thus, a correlation exists between the function of the claimed protein and the structure of the disclosed binding and catalytic domains. Consequently, there is adequate information about which amino acids can vary from SEQ ID NO: 1 and SEQ ID NO: 2

in the claimed genus of amino acids and still provide a polypeptide having activity. Based on the applicant's disclosure and the knowledge within the art, those of ordinary skill in the art would conclude that the applicant would have been in possession of the claimed genus of amino acids based on the disclosure of the species of SEQ ID NO: 1 and SEQ ID NO: 2.

As described in the attached declaration of Qi, the helix structures are well described:



The H-1 and H-5 helices then provide for the ability of the polypeptide to embed within the phospholipid layer of the nanovesicle, providing the biological activity as shown:



In conclusion, the specification satisfies the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the scope of claim 2.

The specification, taken with the pre-existing knowledge in the art of amino acid substitution and the genetic code, would satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the scope of the claims.

As pointed out in the Written Description Training Materials, Revision 1, March 25, 2008, Claim 1 encompasses a genus of any polypeptide having an amino acid sequence selected from the group consisting of the amino acid sequence set forth in SEQ ID NO:1, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions, the amino acid sequence set forth in SEQ ID NO:2, and the amino acid sequence set forth in SEQ ID NO:2 having one or more conservative substitutions; and a pharmaceutically acceptable carrier.

The specification discloses the reduction to practice of SEQ ID NO:1 and SEQ ID NO:2. Although the recitation of a polypeptide with at least 95% identity represents a partial structure -- in that 95% percent of the polypeptide is known, while 5% of the structure may vary, the disclosure of SEQ ID NO:1 and SEQ ID NO:2, combined with the knowledge in the art regarding the genetic code would put one in possession of the genus of polynucleotides that fall within the genus. Further, with the aid of a computer, one could list all of the polynucleotide sequences that with at least 95% sequence identity with SEQ ID NO:1 and SEQ ID NO:2. Additionally, the level of skill and knowledge in the art is such that one of ordinary skill would be able to use conventional sequencing and polynucleotide synthesis techniques to routinely generate and identify the polypeptide of SEQ ID NO:1 and SEQ ID NO:2, as well as those that encode any polypeptide having 95% structural identity to SEQ ID NO: 2. Thus, one of ordinary skill in the art conclude that the applicant would have been in possession of the claimed genus at the time of filing.

The specification satisfies the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the scope of claim 1.

Applicants have provided sufficient detailed examples in the specification showing peptides comprising the amino acid protein depicted in SEQ ID NO:1 and 2 having some

variation. The U.S. Patent Office clearly does not require a description of every embodiment for peptide claims and that while protein chemistry taken as a whole may be unpredictable, particular embodiments are patentable.

It is well-known in the art that the proteins of the invention may be altered in various ways including amino acid substitutions, deletions, truncations, and insertions. Methods for such manipulations are generally known in the art and such variations are easily determined using well known laboratory procedures.

Applicants have provided sufficient detail of particular patentable embodiments and a person skilled in the present art can easily ascertain the sequences that fall within the scope of the present claims.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

The rejection of claims 1-8, 50-57, and new claims 59-63 and 65 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent comprising an anionic phospholipid, particularly phosphatidylserine and a prosaposin polypeptide of SEQ ID NO.1 or SEQ ID NO.2, does not reasonably provide enablement for an agent comprising any and all inner leaflet component, and any and all prosaposin-related polypeptide of an amino acid sequence that is at least 80% identical to SEQ ID NO.1 or 2 is maintained.

Applicants have amended the claims to remove reference to an agent comprising any and all inner leaflet component, and any and all prosaposin-related polypeptide of an amino acid sequence that is at least 80% identical to SEQ ID NO.1 or 2.

Claim Rejections - 35 USC § 112, 1st paragraph (New Matter)

The rejection of claims 50-57 under 35 U.S.C. 112, first paragraph, because of new matter is maintained (it is noted that the rejection made to claims 1-8 and 44-49 is withdrawn in view of applicant's amendment to claims 1 and 44 to cancel the new matter).

Claims 50-57 have now been amended to cancel this matter.

Claim Rejections - 35 USC § 103

The rejection of claims 1 -8, 44-57, and new claims 59-63 and 65 under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993,336(1): 159-162) in view of the teachings of O'brien et al. (WO9503821A1), as evidenced by Vaccaro et al. (FEBS, 1994, 349: 181-186, IDS) is maintained.

As discussed in the Examiner Interview of September 4, the teachings of Vaccaro and O'Brien show forming liposomal vesicles and then adding saposin C to the formulation, resulting in a surface interaction of the protein with the vesicles. A lipid/saposin vesicle formed by this method will not function the same and will not exhibit anti-tumor activity as with the vesicles of the present invention. The claims are also amended to clarify this important feature showing that the prosaposin related polypeptide and the inner leaflet component are combined in an acidic buffer and then treated together to form a nanovesicle exhibiting anti-tumor activity.

The differences are more fully described in the attached declaration by Qi. As discussed, within the present application, each specific example listed in the Examples builds upon the earlier one(s), incorporating all of the same information regarding materials and methods. For example, the description in Example 4 showing the *ex vivo* analysis of effects of saposin C-DOPS on SCC incorporates the tissue culture conditions of Example 3 and the bath sonication of Saposin C and dioleoylphosphatidylserine of Example 2.

Therefore, the application clearly shows that the present invention is not a case of simply a composition comprising a mixture of lipid nanovesicles and polypeptide but is a composition comprising a Saposin-C-DOPS nanovesicle complex. That the composition of the present invention comprises a Saposin-C-DOPS nanovesicle complex and that it would be clear to one skilled in the art from the description of the present invention within the specification, especially as described in Example 2, that the composition comprises a Saposin-C-DOPS nanovesicle complex and not a mixture of nanovesicles and Saposin-C suspended in a carrier.

Claims 44-49, 59-63 and 65 are product by process claims. The claims for a product by process have now been withdrawn although applicant reserves the right to pursue such claims in a further application.

The Examiner has maintained the earlier rejection of claims 1-8, 44-57, and new claims 59-63 and 65 under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993,336(1): 159-162) in view of the teachings of O'brien etal. (WO9503821A1), Vaccaro etal. (FEBS, 1994, 349: 181-186, IDS), and Egas et al. (J. Biol. Chem. 2000, 275(49): 38190-38196).

The Examiner contends that specification teaches that combinations of these two compounds exhibit anti-tumor activity (see page 7, paragraph [0021]). The specification teaches that such composition typically comprise a prosaposin related polypeptide, an inner leaflet component, and a pharmaceutical acceptable carrier (see page 21, paragraph 0071], lines 4-5). The specification teaches that in an embodiment the prosaposin related polypeptide and the inner leaflet component form a nanovesicle, wherein the nanovesicle diameter is in the range of 10 to 10,000 nm (see page 21, paragraph [0071]). Example 6 discloses that administration of an agent comprising saposin C (10 mg/kg body weight) and DOPS (2 mg/kg body weight) to a nude mice bearing human squamous cell carcinoma xenografts inhibited tumor growth (see pages 33-34). Example 6 does not disclose that the agent is in nanoparticle form. Example 9 teaches treating Human SK-Mel-28 melanoma cells with mixtures of Saposin C and DOPS at different molar ratios, and these mixtures of Sap C and DOPS (note: no indication that the mixtures are in nanoparticle from) inhibit tumor cell growth *in vitro*. Therefore, the antitumor activity of the composition does not appear to depend on whether the composition is formulated in nanoparticle form. Moreover, the diameter of the prior art nanoparticle (200-2000 nm) falls within the range disclosed by the specification (10-10,000 nm). In view of the teachings of the specification, the nanoparticles formed between PS SUV and Sap C and between PS LUV and Sap C taught by Vaccaro (1993) would have antitumor activity.

As discussed in the Examiner Interview of September 4, the teachings of Vaccaro and O'Brien show forming liposomal vesicles and then adding saposin C to the formulation, resulting in a surface interaction of the protein with the vesicles. A lipid/saposin vesicle

formed by this method will not function the same and will not exhibit anti-tumor activity as with the vesicles of the present invention. The claims are also amended to clarify this important feature showing that the prosaposin related polypeptide and the inner leaflet component are combined in an acidic buffer and then treated together to form a nanovesicle exhibiting anti-tumor activity.

The differences are more fully described in the attached declaration by Qi. As discussed, within the present application, each specific example listed in the Examples builds upon the earlier one(s), incorporating all of the same information regarding materials and methods. For example, the description in Example 4 showing the *ex vivo* analysis of effects of saposin C-DOPS on SCC incorporates the tissue culture conditions of Example 3 and the bath sonication of Saposin C and dioleoylphosphatidylserine of Example 2.

As such, the Examples 6 and 9 cited by the Examiner are results obtained exclusively using the protein/phospholipids agent in nanoparticle form.

Therefore, the application clearly shows that the present invention is not a case of simply a composition comprising a mixture of lipid nanovesicles and polypeptide but is a composition comprising a Saposin-C-DOPS nanovesicle complex. That the composition of the present invention comprises a Saposin-C-DOPS nanovesicle complex and that it would be clear to one skilled in the art from the description of the present invention within the specification, especially as described in Example 2, that the composition comprises a Saposin-C-DOPS nanovesicle complex and not a mixture of nanovesicles and Saposin-C suspended in a carrier.

Double Patenting

The rejection of claims 1-3, 44-47, 50-52, and new claims 59-61 and 65 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16, 17, 21 and 22 of U.S. Patent No. 6,872,406 in view of Vaccaro et al. (FEBS Lett. 1994, 349:181-186, IDS) is maintained.

A Terminal Disclaimer will be filed if conflicting claims are issued.

Double Patenting

The provisional rejection of claims 1-3, 44-47, 50-52 and new claims 59-61 and 65 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16, 17, 21 and 22 of copending Application No. 10/967,921 in view of Vaccaro et al. (FEBS Lett. 1994, 349:181 -186, IDS) is maintained.

A Terminal Disclaimer will be filed if conflicting claims are issued.

Claim Objections

Claims 44-49, 59-63, and 65 are objected to because of the following informalities: the claims depend from a non-elected invention i.e. claims 58 and 64. The claims have now been amended to remove any inconsistencies.

Claim Rejections - 35 USC § 112, 2nd paragraph

The Examiner has rejected claim 7 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reciting the limitation "the biologically active portion of prosaposin polypeptide". The claims have now been amended to remove any inconsistencies.

Claim Rejections - 35 USC § 112, 1st paragraph

The Examiner has rejected claims1-8, 44-49, 63, and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in reciting the phrases "wherein the nanovesicle has an average diameter in the range of 10-800 nm" recited in claim 1, "wherein the nanovesicle has a diameter in the range 0.01 to 1)nm" recited in claim 63, and "wherein the nanovesicle formed has a diameter in the range 10-800 nm and exhibits anti-tumor activity" recited in claims 44-49 and 65 (limitation from claim 64) are considered new matter since the specification, drawings and claims as filed disclose only the range of 0.01 to 10 um, 0.1 to 1 jam, and 0.1 to 0.5 um. The claims have now been amended to remove any inconsistencies.

CONCLUSION

In light of the amendments and remarks made herein, it is respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited. Applicants encourage the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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